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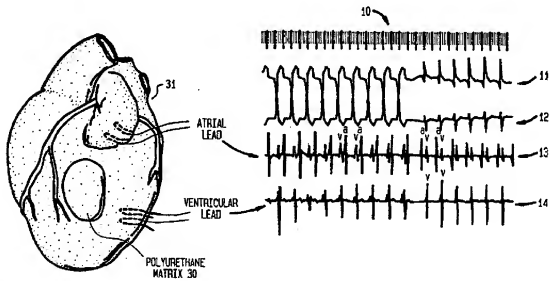

(57) Abstract

A system for controlled release, site-specific delivery of therapeutic agents, particularly myocardial agents such as antiarrhythmic agents, comprises a biocompatible polymeric patch (30) with an incorporated therapeutic agent for direct placement at the epicardium of heart (31). The dosage form is fabricated so as to tailor the release characteristics as required by the nature of the physical condition desired to be treated. In a specific illustrative embodiment, ibutilide, a potent, but toxic, Class III antiarrhythmic agent, is incorporated in polyurethane and solvent-cast to form a monolithic drug delivery device which can be co-implanted with an implantable cardiac defibrillator. Advantageously, very low doses of ibutilide administered directly to the epicardium in this manner produces a reduction in defibrillation threshold.

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SYSTEM FOR CONTROLLED RELEASE OF ANTIARRHYTHMIC AGENTS

Background of the Invention

FIELD OF THE INVENTION

This invention relates to a controlled release dosage form for site-specific delivery of therapeutic agents and, more specifically, to a controlled release dosage form for direct transmyocardial delivery of antiarrhythmic agents either alone or in combination with cardiac rhythm controlling devices and methods of making and using same.

DESCRIPTION OF THE PRIOR ART

Life-threatening cardiac arrhythmias are a medical problem confronting millions of persons daily. Arrhythmias are the principal cause of death following myocardial infarction in hundreds of thousands of other persons. Furthermore, cardiac arrhythmias complicate one-third to one-half of the more than three hundred thousand open heart surgeries carried out annually in the United States. The term "cardiac arrhythmia" is used generally in the art, and herein, to cover conditions of abnormal heart rhythm, and specifically includes ventricular arrhythmia, ventricular fibrillation, and superventricular arrhythmias, such as atrial fibrillation, atrial flutter, superventricular tachycardia, multifocal atrial tachycardia, junctional tachycardia, *etc.*

Currently, the millions of persons suffering from cardiac rhythm abnormalities receive oral drug therapy. Examples of frequently prescribed oral antiarrhythmic therapeutic agents are Digitalis, Digitoxin and Procainamide.

Other antiarrhythmic agents, such as lidocaine or amiodarone are given intravenously. Conventional drug therapy is often ineffective in either preventing or treating life-threatening ventricular arrhythmias due to inadequate drug concentrations where and/or when needed and adverse side effects of the drugs.

In addition to drug therapy, many patients per year now receive intracardiac electronic pacemakers or implantable countershock devices, such as automatic defibrillator/cardioverter devices, for severe cardiac rhythm disturbances. However, there are significant problems created with surgical implantation and subsequent maintenance of electronic pacemakers and implantable countershock devices. In particular, it would be desirable to enhance the function of such devices so that less discharge current is required and the episodes of use are diminished. Lowering the requirements of discharge current would advantageously increase the lifetime of the battery and could facilitate miniaturization.

In general, patients with implantable countershock devices are also treated with antiarrhythmic agents to prevent arrhythmias. However, few of the drugs administered systemically in association with these devices have been shown to be of real benefit for reducing ventricular defibrillation threshold.

Recently, ablative surgical and catheterization techniques have been developed to destroy irritable myocardial tissue; but this has not been particularly effective. Accordingly, drug therapy, pacemaker implantation, and surgery are at best only partially effective for preventing and/or suppressing cardiac arrhythmias.

Sustained site-specific cardiac drug delivery systems have been developed to prevent bacterial endocarditis, to prevent bioprosthetic heart valve calcification and to prevent fibrous tissue buildup. Thyroid and adrenal medulla myocardial autografts were investigated as "endocrinologic cardiac pacemakers." Drug delivery of chronotropic agents has also been accomplished by myocardial implants of silastic reservoirs containing a variety of compounds, including digoxin, isoproterenol, and thyroid hormone, all of which can effectively accelerate cardiac rate when delivered directly into the myocardium.

While these methods have been employed to stimulate and control cardiac rate by transmyocardial drug administration, there have been no examples in the prior art of treatment of ventricular or atrial arrhythmias by transmyocardial administration of antiarrhythmic agents. Nor has there been any disclosure in the prior art of lowering defibrillation threshold in life-threatening fibrillation situations or of increasing resistance to these episodes by transmyocardial delivery of antiarrhythmic agents.

Moreover, none of the above-described polymeric devices can be fabricated so as to have a particular dosage release characteristic. There are obvious advantages to rapid release of the antiarrhythmic agent immediately post-implantation, followed by slower, sustained release, in the treatment of certain conditions, such as acute arrhythmias.

It is, therefore, an object of the invention to provide biological or synthetic polymeric materials which are compatible with body tissues and which

incorporate therapeutic agents, such as antiarrhythmic agents, for the treatment of cardiac rhythm disturbances.

It is a further object of the invention to provide a biocompatible polymeric matrix with incorporated antiarrhythmic agent which can be applied directly to the heart muscle via the epicardium, endocardium, or pericardium.

It is an additional object of the invention to provide a technique for fabricating a biocompatible polymeric matrix with incorporated antiarrhythmic agent wherein the release characteristics of the antiarrhythmic agent can be selectably varied.

It is yet a further object of this invention to provide a biocompatible polymeric matrix with incorporated antiarrhythmic agent which can be applied directly to the heart muscle in conjunction with a cardiac rhythm controlling device to augment the effectiveness of the rhythm controlling devices and/or suppress onset of rhythm disturbances.

Summary of the Invention

The foregoing and other objects are achieved by this invention which provides an arrangement for controlling the heart rhythm of a patient. In accordance with the invention, the arrangement is provided with an electrode for conducting an electrical signal to or from the heart of the patient. An implantable controlled release dosage form releases a therapeutically effective amount of an antiarrhythmic agent to the heart of the patient.

In one embodiment of the invention, a substrate formed of a biocompatible polymeric material has incorporated therein at least one antiarrhythmic agent. In preferred embodiments, the biocompatible polymeric material is a synthetic, nonbiodegradable polymer such as polyurethane, polydimethylsiloxane, ethylene vinyl acetate, polymethyl methacrylate, polyamide, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polytetrafluoro-ethylene, or cellulose acetate. Of course, the polymeric matrix material may be a mixture of two or more biocompatible polymers, or a copolymer.

In alternative embodiments, the biocompatible polymeric material is a biodegradable polymeric material such as collagen, polylactic-polyglycolic acid, or polyanhydride.

The incorporated antiarrhythmic agent may be any therapeutic agent or combination of agents which have an effect on cardiac rhythm disturbances. In some embodiments, the antiarrhythmic agent may be either a cardiac stimulant, such as isoproterenol, dopamine, or norepinephrine or a cardiac suppressant, such as lidocaine. In other advantageous embodiments, the antiarrhythmic agent may be a calcium channel blocker, verapamil or diltiazem. In other advantageous embodiments, and specifically in embodiments used in conjunction cardiac rhythm controlling devices, the antiarrhythmic agent may be prolongers of action potential duration, such as amiodarone, artilide, ibutilide, sotalol, or clofilium. In typical embodiments, the antiarrhythmic agent comprises between about 5% and 40% by weight of the substrate.

Dosage release characteristics may also be tailored in some embodiments by the addition of a pharmacologically inert filler or co-cipient, illustratively polyethylene glycol, inulin, or dimethyl tartrate, which has a water solubility which varies from the water solubility of the antiarrhythmic agent. Advantageously, the anionic tartrate may form an anion-cation pair with a cationic antiarrhythmic agent which serves to retard the release rate. The pharmacologically inert filler is selected from the group consisting of inulin, polyethylene glycol, and dimethyl tartrate.

The substrate is adapted for direct application to the heart of the patient for effecting transmyocardial delivery of the antiarrhythmic agent. The term "transmyocardial delivery" refers to delivery to the heart muscle and specifically also includes contacting the epicardium, endocardium and pericardium. The implantable device may be in any form which may be attached to the heart muscle in some manner such as a patch of film, coated electrode wires, anchorable catheter tip, *etc.* In some embodiments, the electrode is provided with tissue engagement means for engaging the heart tissue of the patient, such as a conical tip.

In some embodiments of the invention, the electrode is further provided with a pacing electrode. In still other embodiments, the electrode is provided with a sensor on a distal end thereof for sensing a predetermined condition of the heart of the patient. The electrode may contain a plurality of defibrillator/cardioverter electrodes.

As stated above, the substrate may be configured in the form of a film, which is some embodiments is fixedly attached to the electrode. The film has a thickness on the order of 20 μm to 1 cm, and preferably about 200 mm. In the alternative, the film may be multilamellar. In other embodiments, the substrate is in the form of a molded cardiac contacting component attached to the electrode means. Certain drug release characteristics can be achieved by molding under compression, illustratively in the range of about 8-10 tons per square inch.

A method of treating cardiac rhythm disturbances in living beings comprises direct controlled release delivery of an antiarrhythmic agent to the epicardium or endocardium by application of an implantable device comprising a polymeric matrix incorporating the desired antiarrhythmic agent.

In accordance with a further aspect of the invention, a cardiac rhythm controlling device is provided with a cardiac contact for conducting an electrical signal to the heart of a living being, and a controlled release dosage arrangement for producing a controlled release of an antiarrhythmic agent.

In accordance with a method aspect of the invention for treating cardiac rhythm disturbances in a living being have a heart, there is provided the step of placing a polymeric matrix incorporating a therapeutically effective amount of at least one antiarrhythmic agent in direct contact with the epicardium or endocardium of the heart of the living being in conjunction with a cardiac rhythm controlling device.

In accordance with this method aspect of the invention, the cardiac rhythm controlling device is an implantable cardioverter-defibrillation device. In some embodiments, the cardiac rhythm controlling device is an implantable pacemaker.

In accordance with a further method aspect of the invention, for treating or preventing ventricular or atrial fibrillation, or ventricular tachycardia, in a living being having a heart, the method is provided with the step of placing a polymeric matrix incorporating a therapeutically effective amount of at least one antiarrhythmic agent of the type which is a prolonger of action potential duration in direct contact with the epicardium of the heart of the living being in conjunction with a cardiac rhythm controlling device.

Brief Description of the Drawing

These and other objects, features and advantages will be better appreciated from consideration of the following detailed description read in conjunction with the accompanying drawings, wherein:

Fig. 1 is a graphical representation of the short term release characteristics of lidocaine-polyurethane matrices fabricated in accordance with the invention and expressed as % cumulative release versus time in minutes;

Fig. 2 is a graphical representation of longer term release characteristics of lidocaine-polyurethane matrices fabricated in accordance with the invention and expressed as % cumulative release versus time in days;

Fig. 3 is a graphical representation of long term release characteristics of lidocaine-polyurethane matrices fabricated in accordance with the invention and

having varying drug loading ratios (wt. lidocaine: wt. polymer precursor) expressed as % cumulative release versus time in days;

Fig. 4 is a graphical representation of short term release characteristics of a lidocaine-polyurethane matrix fabricated in accordance with an alternative embodiment of the invention wherein the matrix mixture was subjected to compression molding expressed as % cumulative release versus time in minutes;

Fig. 5 is a graphical representation of longer term release characteristics of a lidocaine-polyurethane matrix fabricated in accordance with an alternative embodiment of the invention wherein the matrix mixture was subjected to compression molding expressed as % cumulative release versus time in days;

Fig. 6 is a graphical representation of long term release characteristics of a lidocaine-polyurethane matrix fabricated in accordance with an alternative embodiment of the invention wherein the matrix mixture was solvent cast from a solution of dimethylacetamide expressed as % cumulative release versus time in days;

Fig. 7 is an illustrative electrocardiogram of a canine subjected to ouabain-induced tachycardia followed by direct application of a lidocaine-polyurethane patch fabricated in accordance with this invention to the epicardial left ventricular myocardium;

Fig. 8 is a graphical representation of blood plasma level of lidocaine in a canine subject with time for transmyocardial delivery via a lidocaine-polyurethane patch in accordance with this invention;

Fig. 9 is a graphical representation of blood plasma level of lidocaine in a canine subject with time for an intravenous bolus dose of lidocaine, comparable to the transmyocardial dose administered and shown in Fig. 8;

Fig. 10 is a graphic representation of the difference in coronary venous blood levels of antiarrhythmic agent versus systemic blood levels for transmyocardial delivery of lidocaine in a controlled release lidocaine-polyurethane matrices (28% w/w; 44 mg, 5 mm x 5 mm epicardial patches) of the present invention;

Fig. 11 is a graphic representation of an ibutilide-polyurethane matrix exhibiting a burst effect releasing about 30% of the antiarrhythmic agent from a polyurethane matrix in the first 15 minutes, and at a reduced rate thereafter;

Fig. 12 is a graphic representation of the *in vitro* release of the antiarrhythmic agent from an ibutilide-polyurethane matrix containing an inert cocipient, dimethyl tartrate;

Fig. 13 is a graphic representation of is a graphical representation of VERP in ms as measured by an epicardial electrode and an endocardial electrode located proximal to an ibutilide-containing matrix;

Fig. 14 is a graphic representation of the effect on activation time of ibutilide-polyurethane matrices, in milliseconds, the epicardial electrode located proximal to the matrix location;

Fig. 15 is a graphic representation of the probability of successful defibrillation by an implantable cardiac defibrillator for the application of a 2-20 ms monophasic pulse of energy, measured in joules;

Fig. 16 is a graphic representation of the defibrillation threshold for a monophasic pulse before and after administration of 0.025 mg/kg ibutilide;

Fig. 17 is a graphic representation of the defibrillation threshold for a biphasic pulse before and after administration of 0.0025 mg/kg ibutilide;

Fig. 18 is a graphic representation of the % conversion of fibrillation relative to an applied biphasic pulse in joules for the epicardial application of ibutilide-polyurethane matrices having an inert co-cipient therein;

Fig. 19 is a graphic representation of a defibrillation for a clofilium-polyurethane patch upon application of a biphasic pulse from a cardiac defibrillation;

Fig. 20 is a graphic representation of the change in activation time, in milliseconds, as measured by electrodes placed at various distances from the epicardially placed matrix containing sotalol or ibutilide (0.025 mg/kg) as indicated on the drawing;

Fig. 21 is a schematic representation of atrial pacing electrode embodiment of the present invention having a multilamellar ibutilide-containing polyurethane coating;

Fig. 22 is a graphical representation of the long term *in vitro* release characteristics of a dip-coated wire fabricated in accordance with the invention expressed as % cumulative release versus time in days;

Fig. 23 is a bar graph showing the reduction of atrial flutter inducibility by ibutilide-polyurethane coated atrial electrodes of the present invention;

Fig. 24 is a schematic representation of a pacing-transvenous defibrillator catheter having a molded annular conical tip fabricated in accordance with the invention;

Fig. 25 is a graphical representation of the *in vitro* release rate of a molded annular conical tip of the type shown in Fig. 24 expressed as % cumulative release versus time in days; and

Fig. 26 is a graphical representation of the probability of successful defibrillation by a pacing-transvenous defibrillator catheter made in accordance with the present invention.

Detailed Description

A novel controlled release dosage form is described hereinbelow for the therapy of cardiac arrhythmias wherein a substrate comprising a polymeric matrix incorporating at least one therapeutic agent is directly placed in contact with the heart muscle. The therapeutic agent then elutes, or diffuses, directly into the site where it is needed resulting in a rapid conversion from tachycardia to normal sinus rhythms. Direct contact of the dosage form with the heart muscle, either at the epicardium or the endocardium, or in some instances through the pericardium, is herein termed "transmyocardial delivery." A specific advantage of the novel dosage form is that transmyocardial delivery permits a lower dosage of antiarrhythmic agent to be used for localized, or regional, treatment, thereby mitigating the usual adverse side effects of such drugs when administered systemically in doses sufficient to be efficacious.

The polymeric matrix material is illustratively synthetic, such as polyurethane or dimethylpolysiloxane (Silastic). The synthetic polymeric matrix material is preferably flexible, elastomeric, and of great tensile strength so that the resulting controlled release dosage form for transmyocardial delivery will be able to withstand the intense mechanical activity of the heart. In this regard, polyurethane and dimethylpolysiloxane are ideal. High molecular weight polyurethane (*e.g.*, , 40,000 to 80,000 daltons), for example, has desirable surface properties, such as an overall negative surface charge. Advantageously, the negative surface charge binds the cationic antiarrhythmic agents well for sustained release (see, Fig. 2). In particular embodiments, where rapid release of antiarrhythmic agent would be desirable, such as to convert life-threatening arrhythmias to normal sinus rhythm as quickly as possible, hydrophilic polymers, such as polyurethane, are preferred.

Other examples include, without limitation, any biocompatible polymer, whether hydrophilic or hydrophobic, such as ethylene vinyl acetate, polymethyl methacrylate, polyamide, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polytetrafluoroethylene, or cellulose acetate. In an alternative illustrative embodiment, a biologically derived polymer, such as protein collagen, polylactic-polyglycolic acid, or polyanhydride, is a suitable polymeric matrix material.

For certain situations, such as short term arrhythmias associated with cardiac surgeries, biologically degradable polymeric matrices are advantageous since they can be resorbed by the body after a period of sustained drug delivery.

On the other hand, for chronic recurring arrhythmias, nondegradable and/or potentially refillable or renewable, systems, such as a hollow polymeric reservoir, might be more appropriate.

Specific examples of two therapeutic agents, or drugs, which are currently in widespread usage for cardiac rhythmic disturbances and which are well-suited for inclusion in the controlled release dosage form of this invention are lidocaine and amiodarone. Lidocaine is a highly effective antiarrhythmic agent which is typically administered intravenously, and then only for a limited time due to the adverse side effects produced by this agent. Amiodarone can be given orally, but causes severe side effects in over 70% of the patients receiving it. Controlled release dosage forms of the present invention have been formulated to incorporate antiarrhythmic agents from the four generally recognized classes of antiarrhythmic agents (Vaughan-Williams classification). Some examples are given below in tabular form:

Class I - Sodium Channel Blockers

lidocaine
Procainamide
encainide
flecanide

Class II - Beta Adrenergic Blockers

propranolol

Class III - Prolongers of the Action Potential Duration

amiodarone
artilide
bretylium
clofilium
ibutilide
sotalol

Class IV - Calcium Channel Blockers

verapamil
diltiazem
nickel chloride

Lidocaine, for example, is a cardiac depressant. Cardiac stimulants, such as isoproterenol, dopamine, and norepinephrine, can also be incorporated into polymeric matrices in accordance with the principles of this invention and, in some instances, may be used to treat heart failure. An exemplary combination of more than one myocardial agent is the digoxin/quinidine system used to treat atrial fibrillation.

It is to be understood, however, that any antiarrhythmic agent, or combination of antiarrhythmic agents or other drugs which are suitable for co-administration with antiarrhythmic agents, is within the contemplation of the invention. Therefore, the term "antiarrhythmic agent" as used herein means any agent or combination of agents that can be used to treat, or control, cardiac arrhythmias whose mechanism of action conforms to one or more of the four Vaughan-Williams classifications or which otherwise has a therapeutic effect on cardiac arrhythmias.

The antiarrhythmic agents are preferably provided in a water soluble form, such as the hydrochloride salt of lidocaine, to facilitate elution from the polymeric matrix material in the presence of body fluids.

The controlled release dosage forms may be placed directly on the heart muscle during open heart surgery, by cardiac catheter with a detachable tip, or by pericardiocentesis. Three illustrative substrate configurations for cardiac applications include an epicardial design for direct attachment to the surface of the heart which could be in the form of a polymeric film/patch (see Fig. 7), polymer-coated wires (see Fig. 21), or rigid screw-threaded molded polymeric structures. For intravascular placement via a cardiac catheter, a detachable screw-threaded catheter tip, or an expandable (umbrella) system with anchoring prongs (see Fig. 24) are among the many possible configurations which can be devised by one of ordinary skill in the art. Other configurations can be devised for intramyocardial placement via a stab wound with a sharp trochar. Techniques, such as film casting and compression molding, are applicable for fabricating the specific substrate configuration of the antiarrhythmic agent/polymeric matrix controlled release dosage form.

The configuration chosen would depend upon the type of arrhythmia condition being treated. A dosage form in the shape of a patch might advantageously be placed epicardially or endocardially during open-heart surgery to avoid post-operative arrhythmia. A dosage form in the shape of a detachable screw-threaded catheter tip might be utilized to provide prophylaxis against cardiac arrhythmias following myocardial infarction. Moreover, as those of skill in the

art are aware, certain antiarrhythmic agents are more suitable for chronic arrhythmias, for example, than acute arrhythmias, and therefore agents such as procainamide or sotalol would be a drug of choice for incorporation into a controlled release dosage form for application in a chronic arrhythmia situation.

The dosage form may be a monolithic drug/polymer matrix, such as a film or implantable device, from which diffusion-mediated release occurs. In an alternative embodiment, a reservoir-type drug delivery system can be devised. Illustratively, the polymeric matrix material would be configured to form a hollow core reservoir with an access for refilling (see Example 17).

Irrespective of form, the dosage forms of the present invention should preferably have a nonporous, nearly pinhole-free, smooth surface to prevent formation of thrombus and cellular ingrowth. In particular, fibrous or endothelial cellular ingrowth could interfere with efficient release and metabolism of antiarrhythmic agent. Incorporation of an anticoagulant, such as heparin, into the polymeric matrix could minimize thrombus formation.

The novel dosage form would either replace or provide an important adjunct to existing oral or intravenous antiarrhythmic therapy. In addition, the dosage form could be used as part of procedures such as coronary arteriography, angioplasty, routine cardiac surgeries, catheterization and clinical electrophysiology studies. Moreover, inclusion of a dosage form such as described herein would provide additional drug therapy subsequent to pacemaker implantation or could enhance the efficiency of an implanted automatic cardiac defibrillator/cardioverter.

There are various techniques for incorporating the therapeutic agent into the polymeric material matrix of the controlled release dosage form of the instant invention. General illustrative techniques include the following:

1. The therapeutic agent can be combined with the polymeric precursors so that the agent is incorporated as an element of the polymeric mixture prior to solid phase polymerization. Examples 1 and 2 herein are illustrative of this technique.

2. Polymerized matrix material is dissolved in an organic solvent. The therapeutic agent should also be soluble in the same organic solvent so that the therapeutic agent can be added directly to the dissolved polymer matrix material in the desired weight ratio. The mixture is then poured (solvent cast) into a mold, or cast as a film, and the solvent is permitted to evaporate. Examples 3 and 4, for example, are illustrative of this technique.

3. Fully polymerized matrix material can be milled, or mixed, with the therapeutic agent to form a blend which is then polymerized by the addition of a catalyst. Examples 5 and 6 herein are illustrative of this technique.

An advantageous feature of this invention is that drug release rate and duration can be regulated by process parameters. The duration can be varied from minutes to years, depending upon the formulation conditions of the polymeric matrix. The parameters which may be varied to control release rates include particle size of the therapeutic agent, disruption of the polymerization process with stirring, compression molding, and temperature of polymerization. The specific examples described hereinbelow illustrate the effects of some of

these parameter variations. The results are graphically depicted in Figs. 1-6. In other embodiments, the release rate is varied by the addition of a pharmacologically inert co-cipient, such as described in Example 14, Formulation 14b, and shown graphically on Fig. 12. In still further embodiments, configuration, such the provision of multiple layers, can affect the drug release rate as shown graphically on Fig. 22.

Release characteristics of the drug-polymer combination can also be made responsive to feedback signals. An electrically responsive acrylamide polymer or silicone rubber containing a cation-exchange resin, for example, could be made to provide more drug when arrhythmia is detected and then to down-regulate when the abnormal rhythm has ceased. Such an electrically responsive embodiment would be particularly useful in conjunction with a cardiac rhythm controlling device.

Given below are several specific illustrative embodiments of biocompatible controlled release dosage forms in accordance with the invention and methods of making same. Also included are experimental results showing the efficacy and advantageous features of the dosage form under *in vitro* and *in vivo* conditions. Although Examples 1-5 are primarily directed to the preparation of polymeric matrices incorporating the antiarrhythmic agent lidocaine, the techniques described herein are applicable to the creation of a wide variety of other drug/polymer combinations and devices formed thereof. Additional examples (Examples 6 to 17) demonstrate that controlled release dosage forms in accor-

dance with the principles of the invention have been fabricated to incorporate antiarrhythmic agents from all four classes of antiarrhythmic agents.

Example 1:

Lidocaine-polyurethane matrices were prepared by mixing about one to four parts of lidocaine hydrochloride (particle size 75-150 μm) with ten parts of Tecoflex 2-80A (a polyurethane prepolymer made by Thermedic Inc., Woburn, MA) comprising 0.21 parts of diisocyanate monomer and 0.79 parts of polyether monomer.

In the lidocaine/polyurethane example, prepolymerized polyurethane components will not react to form polymer in the presence of more than about 20% by weight of the antiarrhythmic agent. However, a $FeCl_3$ catalyst and slow curing at low temperatures will result in the formation of a stable polymer. In general, 0.1 μM to 1.0 μM $FeCl_3$ per g of polyether monomer is effective to provide a viable polymeric structure with up to 40% w/w drug loading. Advantageously, the resultant antiarrhythmic agent-polymer matrix will release antiarrhythmic agent with an accelerated early rate followed by a sustained, slower diffusion-controlled rate. The accelerated early rate is particularly advantageous in the treatment of acute arrhythmic disturbances.

In the specific illustrative embodiment of Example 1, 0.74 μM $FeCl_3$ per gram of polyether monomer was added as a catalyst. The mixture was then cast as a film of approximately 200 μm thickness and cured for 48 hours at 55° C. Of course, film thicknesses can vary, as a practical matter such thicknesses range from about 20 μm to 1 cm. Temperature and time ranges for polymerization can

also range, respectively, from about 50° C to 60° and from about 24 hours to 3 days.

a) *In Vitro* Experiments:

Cumulative drug delivery *in vitro* of 28% w/w loaded lidocaine-polyurethane matrices, fabricated by the technique of Example 1, was monitored spectrophotometrically by absorbance at 260 nm. Samples of a perfect sink buffer solution were taken over time and the data was expressed as the means of duplicate measurements. The perfect sink buffer solution comprised 0.54 M aqueous K_2PO_4 at a pH of 7.4 and temperature of 37° C.

Figs. 1 and 2 show the results of certain process variations to the method of Example 1 which affect the release of lidocaine. These process variations are (1) polymerization at 55° C as described in Example 1; (2) an additional step of stirring the polymerization mixture after about 2 hours (post-long chain polymerization and pre-crosslinking) of reaction time; and (3) polymerization at room temperature. Referring specifically to Fig. 1, the short term release characteristics are graphically shown as a plot of % cumulative release versus time in minutes. Line 1 represents the release characteristics of the matrix formed in accordance with the process described in Example 1 (process variation (1) above); line 2 represents process variation (2) above; and line 3 represents process variation (3) above.

Fig. 2 is a graphical representation of long term release characteristics shown as a plot of % cumulative release versus time in days. Lines 1 through 3

represent the release characteristics of the matrices formed in accordance with processes (1) through (3), respectively.

The *in vitro* results show that variations in process parameters do affect the drug release characteristics of the drug/polymer matrix. In the polyurethane system of Example 1, the use of a higher molecular weight polyol in the polymer segments resulted in a more hydrophobic product, and hence a product capable of greater retention of the drug over time.

In other experiments, the effect of various drug loading ratios was examined *in vitro*. Reference to Fig. 3 shows a graphical representation of long term release characteristics of lidocaine/polyurethane matrices having varying weight ratios of lidocaine to polyurethane. The data was obtained by spectrophotometric absorbance measurements and is expressed as % cumulative release versus time in days. The particular ratios examined were 2:10, 3:10, and 4:10 which are represented on Fig. 3 as lines 1, 2, and 3, respectively. The release rate profiles consisted of higher initial rates than the longer term diffusion-controlled rates. Moreover, as drug concentration was increased, initial rates increased while the diffusion-controlled rates remained about the same.

Example 2 :

A lidocaine-polyurethane matrix combination was prepared in accordance with the method of Example 1. However, after a period of about 2 hours, when long chain polymerization was essentially completed, but prior to crosslinking, the reaction mixture was stirred for a short period of time, in this specific example, for 5 minutes.

This mixture was then compression molded under 8-10 tons per square inch. The long and short term release characteristics *in vitro* of the resultant dosage form are shown in Figs. 4 and 5 as a function of % cumulative release versus minutes and days, respectively. Compression molding markedly decreases the release rate.

Example 3:

A lidocaine-polyurethane matrix combination was prepared by a solvent casting technique. Fully polymerized polyurethane was dissolved in an organic solvent, such as to form a clear, liquid solution. The desired amount of lidocaine was added into this solution. The solution was then cast as films 2-4 mm in thickness.

Fig. 6 is a graphical illustration of the long term release characteristics for the solvent cast dosage form fabricated in accordance with this Example. This *in vitro* experiment was conducted at pH 7.4 in the same manner as described hereinabove with respect to Example 1. Comparing the results of Fig. 2 with Fig. 6, it is observed that the solvent casting technique results in a greater prolongation of sustained release of the therapeutic agent.

A polymeric matrix of the type described hereinabove was used to demonstrate the effective transmyocardial administration of lidocaine by direct placement of a patch of said matrix on the epicardial surface of a canine heart. The following experiment details the inhibition of ouabain-induced ventricular tachycardia with epimyocardial implants of the controlled release lidocaine-polyurethane matrix system fabricated in accordance with Example 1.

b) *In Vivo* Experiments:

Ventricular tachycardia was induced with ouabain administration in accordance with a method described in an article by Kniffen, *et al.*, Circulation, Vol. 49, page 264, 1974. Ouabain is a cardiac glycoside which is used therapeutically for its rapid digitalizing effect. The experiment involved 14 male mongrel dogs weighing from 12-14 kg each. Ouabain obtained from Sigma Inc., St. Louis, MO, was administered at an initial dose of 40 micrograms/kg at a rate of 40 micrograms/minute, and at subsequently halved dosages until sustained ventricular tachycardia was documented by electrocardiogram.

Each dog was subjected to a left thoracotomy in order to induce ventricular tachycardia with administered ouabain. Referring to Fig. 7, a polymeric patch 30 having dimensions of 3 cm x 3 cm x 0.2 cm was applied to the epicardial left ventricular myocardium of heart 31 about 1-2 cm to the left of the anterior descending coronary artery, about 1-2 cm below the circumflex coronary. Fig. 7 is also illustrative of an electrocardiogram obtained as a result of this experiment. Electrocardiographic configuration was obtained with standard surface limb leads, as well as atrial and ventricular leads. Recordings from the limb leads are shown at 11 and 12 and atrial and ventricular deflections are 13 and 14, respectively. Conversion of ventricular tachycardia after placement of a lidocaine-polyurethane matrix to normal sinus rhythm is indicated by arrow 10. In each animal, the lidocaine-polyurethane matrix patch 30 was left in place on the left ventricular myocardium for the time needed to convert the ventricular tachycardia to normal sinus rhythm. When normal sinus rhythm reappeared,

patch 30 was removed after one minute had elapsed, and the experiment was continued in order to detect the return of the induced arrhythmia. Some dogs had patches of polyurethane only as controls.

Ouabain-induced ventricular tachycardia in the dog was converted to normal sinus rhythm in all experimental animals studied via controlled release drug delivery of lidocaine from a polymeric matrix attached directly to the ventricular myocardium as shown in Table I wherein time is given in terms of mean ± standard error.

TABLE I

Polymer Application	Number or Animals In Ventricular Tachycardia		Time (min)
	Initial	Final	
Polyurethane	4/4	4/4	>60
Lidocaine/Polyurethane	6/6	0/6	1.5 ± 0.77
Removal of Lidocaine/ Polyurethane	0/6	3/6	15.0 ± 25.0

The results given in Table I for the time range for return of ventricular tachycardia after removal of the lidocaine-polyurethane matrix is for three animals. The remaining three animals continued in normal sinus rhythm for greater than 60 minutes. In animals with the control patches, ventricular tachycardia continued for more than 60 minutes without the resumption of normal sinus rhythms. The lidocaine-polyurethane patch converted the ventricular tachycardia to normal sinus rhythm in 1.5 ± 0.77 minutes.

Dog studies analyzing blood plasma levels of lidocaine indicated that myocardial application of a lidocaine-polyurethane patch resulted in therapeutic effects as rapidly as lidocaine administered intravenously by bolus dose, but with comparatively lower plasma levels as determined by high performance liquid chromatography. Referring to Fig. 8, lidocaine plasma levels in the canine study are shown as the means of duplicate measurements for plasma levels in six dogs and their time-dependent decay after epicardial lidocaine-polyurethane therapy. In comparison, Fig. 9 shows plasma levels for 2 dogs following intravenous administration of 24 mg/kg and 45 mg/kg doses of lidocaine. The intravenous dosage levels were chosen to correspond to approximately the same dosage level as epicardial administration achieved by the polymeric patch as determined by sohxlet methanolic extraction of the residual drug remaining in the polymeric matrices after *in vivo* use, followed by subsequent high performance liquid chromatography utilizing a Waters Model 6000A system (Waters, Inc., Bedford, MA) with a prepacked C18 column (particle size 5 μm), Altex ultrasphere-ODS 25 cm x 4.6 mm I.D. (Beckman Inc., San Ramon, CA) and an isocratic mobile phase of 0.1M sodium phosphate buffer at pH 3.0 with 0.7% v/v triethylamine-acetonitrile (50:50). Absorbance was monitored at 210 nm.

The above-described experimental results demonstrate that transmyocardial site-specific drug delivery is an effective route for the administration of antiarrhythmic therapy. The direct epicardial placement of lidocaine-polyurethane controlled release matrices resulted in the prompt conversion of induced arrhythmia to normal sinus rhythm in all experimental animals studied in about

1.5 minute, while controls had persistent ventricular tachycardia for more than 60 minutes. Site specific therapy was as rapid as intravenous administration, yet resulted in lower plasma lidocaine levels for comparable dosages.

In a study conducted on the transmyocardial delivery of lidocaine-loaded polyurethane patches attached to the epicardia of dogs, net doses of between 19 mg/kg and 45 mg/kg of lidocaine were delivered. However, the plasma levels of lidocaine were 8.75 to 25 μg/ml for the controlled release dosage form of the present invention as compared to 36.7 to 101.2 μg/ml following administration of a comparable dose intravenously. Thus, the direct myocardial placement of the dosage form described herein would mitigate adverse side effects of lidocaine, or any other antiarrhythmic agent administered in that manner.

Example 4:

Lidocaine has been incorporated into an ethylcellulose matrix by a solvent casting technique using various solvents, including chloroform, methylene chloride, and ethylacetate. The lidocaine loading ratio was 2:10.

Example 5:

Lidocaine in a silastic matrix was made by blending fully polymerized Silastic 382, a trademark of Dow-Corning, Midland, MI, with lidocaine. In the instant case, 5% lidocaine by weight was added to the Silastic. This blend was polymerized by the addition of a stannous octanoate catalyst.

Example 6:

An isoproterenol-polydimethylsiloxane matrix dosage form has been fabricated and found to produce efficacious results. Pre-polymerized polydi-

methylsiloxane (PDMS) was milled together with powdered isoproterenol (5-20% by weight relative to the weight of PDMS) to form a blend. The blend was then catalyzed, either by heat or by addition of a chemical such as stannous octanoate or platinum oxide, and permitted to polymerize.

Controlled release matrices having antiarrhythmic agents from the four Vaughan-Williams classifications of antiarrhythmic agents have been formulated in various polymeric matrices. Specific illustrative examples are set forth hereinbelow. The Class I sodium channel blockers, such as lidocaine, procainamide, encainide, and flecanide, are represented in Examples 1-5 hereinabove.

Example 7:

A Class II (beta adrenergic blockers) antiarrhythmic agent, propranolol, has been incorporated into various polymeric matrix materials, particularly polyurethanes, such as Mitralthane MPU-5 (a polyurethane available from Symbion, Denver, CO) or biomer (a polyurethane available from Ethicon, Somerville, NJ), in amounts of up to 30% wt/wt. in accordance with the method of Example 3.

Example 8:

Class III antiarrhythmics, which prolong the action potential duration, are represented by amiodarone (available from Wyeth, Philadelphia, PA) in specific illustrative embodiments.

Amiodarone has been incorporated in a polyurethane matrix by the method of Example 3. More specifically, amiodarone was dissolved in dimethylacetamide to form a solution having a concentration of 100 mg/ml therapeutic

agent. This solution was further dissolved in a 10% solution of polyurethane (Thyomer, Thermedics, Inc., Woburn, MA) with polyethyleneglycol (PEG 200, Dow, Midland, MI) as a 10% co-cipient. This solution was solvent cast into a 0.2 mm film and used in the studies reported below in Table II. Polyethylene glycol facilitates the release of the amiodarone from the polyurethane matrix.

In addition to amiodarone, artilide has been incorporated into a polyurethane matrix by the solvent casting technique of Example 3. Artilide is a Class III antiarrhythmic agent that is structurally related to sotalol and ibutilide. Artilide, like ibutilide, does not block beta adrenergic receptors and prolongs action potential duration and refractoriness by an ionic mechanism which differs from other Class III drugs, such as sotalol.

Example 9:

Another Class III antiarrhythmic agent, d-sotalol (Bristol-Meyers Squibb, Wallingford, CT) was incorporated into polyurethane (Mitralthane MPU-5) in accordance with the procedure of Example 3 and used in the canine study reported hereinbelow in Table III.

In yet another embodiment, d-sotalol was dispersed in levigated silicone rubber (Silastic Q7-4840; 1:1) to form a composite. In a specific illustrative example, the composite was compressed in a stainless steel slab mold at 2000 pounds per square inch for one minute. The compressed composite was cured for 24 hours at 37° C.

Example 10:

Class IV antiarrhythmic agents, or calcium channel blockers, including verapamil, diltiazem, and nickel chloride have been incorporated into various polymeric matrix materials, such as polyurethanes such as Mitralthane MPU-5, and silastics such as Q7-4850 in accordance with a solvent casting technique as described in Example 3.

Example 11:

Antiarrhythmic agents have been incorporated into exemplary biodegradable matrices such as a high molecular weight polyanhydride, polysebacic acid-carboxyphenoxy propane (Nova, Baltimore, MD) and purified rat tail collagen. Films can be cast from the anhydride by dissolving it in methylene dichloride. The collagen may be cast from a solution in 0.1M acetic acid.

In a specific embodiment of a biodegradable matrix, sotalol was formulated into a poly (*dl*-lactide-co-glycolide) (PLGA) matrix by an "in water" drying technique as reported by Ogawa, *et al.*, J. Pharm. Pharmacol., Vol. 41, pages 439-444 (1989). In a typical procedure, 800 mg sotalol and 100 mg gelatin were dissolved in 1 ml water in a 60° C water bath. The drug solution was emulsified with a polymer solution by sonification (Model W-225R, Heat Systems-Ultrasonics, Inc. Farmingdale, NY) at 30 Hz for 15 minutes in an ice bath. The polymer solution comprised 1.8 g PLGA dissolved in 20 ml methylene chloride. This emulsion was added drop-wise with continuous stirring (Stir-pak, Cole Parmer Instrument Co., Chicago, IL) at 400 rpm into 200 ml of 1% w/v polyvinyl alcohol (PVA) adjusted to a pH of 9.0 with sodium phosphate dibasic

and saturated with methylene chloride. After 1 hour of stirring, the emulsion was added into 2 liters of aqueous 0.1% w/v PVA solution (pH = 9.0) and stirred for an additional 3 hours. The microspheres so formed were passed through a #100 mesh sieve. The fraction remaining on the #400 mesh sieve were recovered by centrifugation, washed four times with distilled water, lyophilized for 48 hours, and then dried under vacuum for 48 hours.

In an illustrative example of use, the sotalol-PLGA microspheres can be suspended in a saline solution, for example, and injected into a space prepared in the pericardium.

Example 12:

In Vivo Ventricular Pacing Studies

Ventricular tachycardia was induced and maintained by rapid ventricular pacing in an open-chest dog model using male mongrel dogs (10-15 kg). Three sets of bipolar epicardial electrodes were placed at 2 cm distances from the left ventricular apex toward the base of the heart. A Grass Model 8 stimulator (Grass Instruments, Quincy, MA) delivered continuous electrical stimulation as 2-msec square wave impulses with a 50-msec cycle length via a stimulus isolation unit (Bloom Associates, Reading, PA). The stimulus isolation unit also repeatedly monitored the pacing current thresholds. After induction of ventricular tachycardia, a controlled release dosage form of the present invention in the shape of a patch of the drug-loaded polymeric matrix material was placed adjacent to the stimulating electrode. The time required to convert the ventricular tachycardia to sinus rhythm was measured, as well as the time course of the quantitative change

for sustaining the induction of ventricular tachycardia. The results are reported below in Table II. The effects of controlled release were monitored for up to 4 hours after conversion to normal sinus rhythm.

The lidocaine-Tecoflex patch was manufactured in accordance with Example 1 hereinabove. All other dosage forms were fabricated by dissolving the therapeutic agent in dimethylacetamide at a concentration of 100 mg/ml therapeutic agent. This solution was further dissolved in a 10% solution of a Thyomer polyurethane and solvent cast into a 0.2 mm films. Amiodarone matrices were cast with polyethyleneglycol as a 10% cocipient as described in Example 8. Controls comprised patches of each polymeric matrix material.

Table II
Transmyocardial Controlled-Release Conversion of Ventricular Tachycardia (VT) Induced by Rapid Ventricular Pacing

Agent	No.	Polymer Matrix	Drug Loading	Conversion (minutes)	Peak % Increase in VT Threshold
Lidocaine	16	Tecoflex	28%	0.86 ± 0.68	367.7 ± 183.1
Procainamide	7	Thyomer	30%	4.05 ± 3.15	206.7 ± 172.6
Amiodarone*	3	Thyomer	30%	5.90 ± 5.45	36.1 ± 12.7
$NiCl_2$	4	Thyomer	50%	2.08 ± 1.71	122.6 ± 101.3
Control	5	Tecoflex	0.0	no effect	no effect
Control	2	Thyomer	0.0	no effect	no effect
Control	1	Thyomer*	0.0	no effect	no effect

*with 10% polyethylene glycol, PEG 200; Data as mean ± standard error.

Referring to Table II, the site-specific application permitted the lidocaine-containing form to be effective at net dosages of only 0.1 mg/kg. Moreover, peripheral plasma levels of lidocaine were undetectable despite effectiveness in converting tachycardia to normal sinus rhythm. Other studies revealed that

lidocaine administered by this route created no other significant effects on normal cardiac function.

Procainamide was also effective in converting ventricular tachycardia in the ventricular pacing model.

Amiodarone is a highly effective antiarrhythmic agent which is frequently associated with severe side effects. It efficacy when utilized in the controlled release dosage form of the present invention demonstrates that the transmyocardial route of administration may be the safest and most effective manner of delivering this drug.

Nickel chloride is an example of a prototype drug system which would be difficult to administer systemically, but which has shown promise as an antiarrhythmic. However, the results of Table II show that nickel chloride is effective to convert tachycardia to normal sinus rhythm by direct epicardial application in the controlled release dosage form of the present invention.

A pharmacokinetic study performed with controlled release the lidocaine-polyurethane matrices (28% w/w; 44 mg, 5 mm x 5 mm epicardial patches) demonstrated the significance of site-specific application of the controlled release dosage of the instant invention. Fig. 10 is a graphic representation of the difference in coronary venous blood levels of antiarrhythmic agent versus systemic blood levels.

The lidocaine-polyurethane matrix was placed on the left ventricular epicardium of dog adjacent to the pacing electrode. Lidocaine plasma levels were measured by a high performance liquid chromatographic assay in samples

obtained over a 4 hour period of epicardial matrix application. Referring to Fig. 10, a total dose of 920 μg/kg was delivered. Regional coronary venous plasma levels of lidocaine were in the range of 0.8-2.3 μg/ml while simultaneously sampled peripheral blood levels were about 100-fold lower, or 5.4-20.3 ng/ml).

Example 13:

In Vivo Ischemia-Induced Ventricular Tachycardia Studies

Controlled release dosage forms of the present invention have been successful in preventing ischemia-induced ventricular tachycardia in a canine model. Ventricular occlusions of the left anterior descending coronary artery of a dog were produced by exposing and isolating the artery in a dog under anesthesia. A snare with a sliding closure was placed around the artery. Ventricular tachycardia was produced by closing the snare for 10 minutes to shut off the blood supply to left ventricle. The snare was opened for an hour, and then the snare was closed for 10 minutes. This procedure can be repeated up six times and simulates a heart attack. Ventricular tachycardia (VT) was defined as the occurrence of 3 or more sequential ventricular premature beats. The efficacy of various controlled release dosage forms of the present invention were documented by continuous recording of the electrophysiologic data on a Hewlett Packard Physiologic Records, and an 8-channel analogue tape deck (Hewlett Packard, Philadelphia, PA). The results are shown in Table III.

TABLE III

Antiarrhythmic Controlled Release Therapy: Results of Acute Ischemia-Ventricular Tachycardia (VT) Studies in Dogs

Drug	Mechanism	Polymer	Loading	Dose (mg/kg/2hr)	N	VT (per/minute)
Lidocaine	Na Channel Blocker	Tecoflex	28%	0.23	5	0.6±0.2
Propranolol	Beta Blocker	MPU-5	30%	0.14	6	1.22±.12
D-Sotalol	Delayed Re-polarization	MPU-5	30%	0.20	9	.046±.11
Verapamil	Calcium Channel Blocker	MPU-5	30%	0.30	11	0.10±.03
No Therapy	—	Control	—	—	9	1,10±0.30

Referring to Table III, the total dose over a 2 hour period (mg/kg/2hr) for the various drug-loaded matrices was estimated from *in vitro* release data which has been found to correlate well with *in vivo* release rates. The data is expressed as the average for the number N of dogs per group. Episodes of VT were paced at one per minutes. Table III shows the number of VT episodes per minute following epicardial placement of the identified drug-loaded matrix. The Class II calcium channel blocker, verapamil, and the Class III agent, D-sotalol, were the most effective for arrhythmias due to acute myocardial ischemia. Interestingly, verapamil is contraindicated for arrhythmias when given systemically. However, Table III demonstrates the effectiveness of verapamil for transmyocardial delivery.

Example 14:

In Vivo Electrophysiologic and Defibrillation Threshold Studies

In an advantageous application of the principles of the invention, antiarrhythmic agent-containing controlled release dosage forms of the present invention are used in conjunction with a cardiac defibrillator. Epicardial delivery of Vaughan-Williams Class III antiarrhythmic agents has been shown to decrease defibrillation threshold in dog studies.

Implantable cardiac defibrillators, such as the automatic cardiac defibrillator marketed by Cardiac Pacemakers, Inc., Minneapolis, MN, (see, for example, U.S. Patent Nos. 3,614,954 and 3,614,955) are well known for the purpose of applying a direct current to the heart in life-threatening or chronic situations.

Implantable cardiac defibrillators comprise a miniaturized power source, two bipolar lead systems, and a computer chip which is an electrocardiogram sensing mechanism for discharging monophasic or biphasic electrical pulses through the electrode leads for short durations (usually 2-20 ms). In one embodiment, a lead is placed transvenously via a catheter in the endocardium of the right ventricle and the second lead comprises an array of electrodes which are placed subdermally. A maximum of approximately 20 to 25 joules is typically required to restore normal heart rhythm. In other embodiments, both electrode leads may be placed directed on the epicardium or endocardium of the right and left ventricles of the heart during open heart surgery. In this embodiment, typically 5 joules of energy is required to restore normal heart rhythm.

While the implantable cardiac defibrillators have been used successfully, it would be desirable to enhance their function so that less discharge current is required and the episodes of use are diminished. Lowering the requirements of discharge current would advantageously increase the lifetime of the battery and could facilitate miniaturization.

The Class III drugs are prolongers of cardiac action potential duration. Several newly developed potent Class III drugs are toxic when administered intravenously or by other known techniques. These agents include ibutilide, clofilium, and sotalol. Ibutilide, for example, has been shown to be effective against atrial and ventricular arrhythmia in dogs and atrial arrhythmia in humans. Action potential duration (APD) studies in dogs has also shown that ibutilide increases the action potential duration at very low doses and elevates the plateau height.

Studies were conducted to assess electrophysiological effects and defibrillation threshold when the aforementioned Class III drugs were incorporated into the controlled release delivery system of the present invention and applied epicardially to dogs during defibrillation. In the studies reported hereinbelow, a monolithic controlled release matrix was co-implanted with the implantable automatic cardiac defibrillator. However, it is anticipated that the drug-loaded matrix can be integrated directly with an automatic implantable cardiac defibrillator, such as by coating the electrode leads with the drug-loaded polymeric matrix material (see Fig. 21).

For the following *in vivo* studies, drug-loaded matrices were prepared as follows:

Formulation 14a:

Antiarrhythmic agent and Pellathane™ polyurethane (a high molecular weight polyurethane sold by Dow Chemical Company, Midland, MI) were dissolved in THF and solvent cast in a Teflon-coated mold to form films of 50-60 μm thickness. A quantity of antiarrhythmic agent sufficient to result in 20% wt./wt. drug-loading was used.

In a specific illustrative embodiment, 100 mg ibutilide fumarate and 400 mg polyurethane were dissolved in 10 ml THF and stirred for 60-90 minutes in a closed vial. Following solvent casting, the cast films were placed in a fume hood so that the solvent could evaporate at room temperature for about 48 hours.

Formulation 14b:

The release kinetics of the resulting drug-matrix was varied by replacing a certain proportion of the antiarrhythmic agent with an inert, *i.e.*, non-pharmacologically active, co-cipient or filler with a lower water solubility, such as inulin or dimethyl tartrate. In the specific formulations used in the present studies, 16% wt./wt. dimethyl tartrate and 4% wt./wt. ibutilide was incorporated in a Pellathane™ polyurethane matrix. However, it is to be understood that the proportion of antiarrhythmic agent to filler can be varied to achieve a desired effect. Dimethyl tartrate, for example, is also organically soluble.

In this specific illustrative embodiment, 20 mg ibutilide fumarate, 80 mg dimethyl tartrate and 400 mg polyurethane were dissolved in 10 ml THF and

solvent case to yield matrices with weights and dimensions similar to the matrices obtained in Formulation 14a.

In vitro release studies were conducted in phosphate buffered saline (pH 7.4) at 37° C under perfect sink conditions. The matrix specimens were placed in the buffered solution on a rotary shaker (110 rpm) and the drug levels were monitored spectrophotometrically at 227 nm. Matrices fabricated in accordance with Formulation 14a have an initial burst effect releasing about 30% of the antiarrhythmic agent in the first 15 minutes and at a decreased rate so that there is about 40% depletion by 120 minutes as shown in Fig. 11. In contrast, matrices fabricated in accordance with Formulation 14b release only about 9.6% of the antiarrhythmic agent during the first 15 minutes followed by an almost linearly increasing rate until about 17.1% depletion is achieved at 120 minutes as shown in Fig. 12. Thus, the dose administered over a given time period can be lowered by retarding the release rate in this manner.

Standard (14 cm^2) defibrillation electrodes were placed over the left and right ventricles of the heart of a dog. In order to cause fibrillation, an epicardial electrode (Bloom stimulator, Bloom Associates, Reading, PA) was sewn into the left ventricle to deliver an electrical impulse (T = 10 ms). A pair of recording electrodes were placed in the right ventricle to measure electrophysiological changes. Test shocks were delivered in a random sequence to determine baseline defibrillation threshold (DFT). The drug-loaded matrix (1.5 cm x 1.5 cm patch weighing about 25-28 mg) was placed in the anterior left ventricle and DFT studies were conducted for a 2 hour period post-implantation.

Epicardially placed ibutilide-polyurethane matrices (Formulation 14a) had a significant effect on electrophysiological parameters. The ventricular effective refractory period (VERP) changed from a baseline, in milliseconds (ms), of 124.9 ± 3.3 - 136.0 ± 1.71 to 151.7 ± 3.4 - 154.6 ± 3.5 at an epicardial electrode located proximal to the matrix location. At an endocardial electrode located proximal to the matrix location, the baseline changed from 129.1 ± 2.2 - 137.3 ± 2.1 to 148.0 ± 1.7 - 152.0 ± 4.7. See Fig. 13 which is a graphical representation of VERP in ms as measured by an epicardial electrode and an endocardial electrode located proximal to the ibutilide-containing matrix. Similar changes were recorded for VERP at an endocardial electrode placed distal to the matrix location.

The same ibutilide-polyurethane matrices (Formulation 14a) had a significant effect on activation time (AT). Referring to Fig. 14, AT, in milliseconds, changed from a baseline of 27.1 ± 1.4 - 27.1 ± 1.7 ms to 65.1 ± 6.2 - 71.8 ± 6.9 ms at the epicardial electrode located proximal to the matrix location. At the endocardial electrode located proximal to the matrix location, the baseline changed from 27.1 ± 1.4 - 27.1 ± 1.7 to 50.2 ± 7.2 - 54.2 ± 7.1. Changes in AT of the same magnitude were recorded at an endocardial electrode placed distal to the matrix location.

The defibrillation threshold (DFT) was significantly decreased after application of the ibutilide matrices (Formulation 14a). Fig. 15 is a graphical representation of the probability of successful defibrillation by an implantable cardiac defibrillator for the application of a 2-20 ms monophasic pulse of energy,

measured in joules. Referring to Fig. 15, the control data represents defibrillation prior to the administration of ibutilide. Following epicardial attachment of an ibutilide-polyurethane matrix in accordance with Formulation 14a, the energy associated with an 80% probability of successful defibrillation (DFT 80) decreased from 15 joules at baseline to 3.9 joules after epicardial administration of the ibutilide matrix. DFT 90 decreased from about greater than 20 joules to 4.9 joules. No changes in heart rate or arterial pressure were observed. The ibutilide-polyurethane matrix dispensed a 0.025 mg/kg dose over the experimental period ($p < 0.001$, paired t-tests).

The estimated dose of ibutilide released from the matrix over the 2 hour experimental period was 0.025 mg/kg. This small dose, when applied to the epicardium, produced a 4-fold decrease in DFT. Dose response studies were conducted and it was noted that ibutilide is effective to reduce DFT at a dose as low as 0.0025 mg/kg.

For comparative purposes, defibrillation threshold was measured following intravenous administration of ibutilide at equivalent doses (0.25 mg/kg and 0.0025 mg/kg). The results are shown on Figs. 16 and 17 which are graphical representations of the probability of successful defibrillation for an application of a 2-20 ms pulse of energy in joules. Fig. 16 shows the DFT for a monophasic pulse before and after administration of 0.025 mg/kg ibutilide. Fig. 17 shows the DFT for a biphasic pulse before and after administration of 0.0025 mg/kg ibutilide.

Ibutilide-polyurethane matrices in accordance with Formulation 14b were applied to the epicardium of dogs in conjunction with standard implantable cardiac defibrillator electrode. Fig. 18 is a graphical representation of the % conversion of fibrillation relative to an applied biphasic pulse in joules.

In another embodiment, clofilium-containing polyurethane matrices were made in accordance with the procedure set forth in Formulation 14a. This resulted in a 2 mg/kg dose of clofilium released over the experimental 2 hour period. Referring to Fig. 19, a decrease in DFT 80 from about 18.5 joules to 14.7 joules is observed when a clofilium-polyurethane patch is co-implanted with an implantable cardiac defibrillator electrode and a biphasic impulse is used to defibrillate induced fibrillation.

In a still further embodiment, 20% wt./wt. sotalol was incorporated into a polyurethane matrix in accordance with the procedure set forth in Formulation 14a. This resulted in an 0.8 mg/kg dose of sotalol over the experimental 2 hour period. Fig. 20 shows the change in activation time, in milliseconds, as measured by electrodes placed at various distances from the epicardially placed matrix containing sotalol or ibutilide (0.025 mg/kg) as indicated on the drawing.

In conclusion, ibutilide-polymer matrices as well as other formulations (specifically including formulations containing clofilium and/or sotalol) were successfully fabricated and demonstrated to have Class III electrophysiologic effects (*i.e.*, prolongation of refractoriness and conduction velocity), which will be beneficial for preventing ventricular arrhythmias. The controlled release epicardial implants of the present invention have been demonstrated to be superior

to intravenous administration of the drugs both in terms of potency and sustained electrophysiologic effects.

The ibutilide-polyurethane matrices used as cardiac implants also produced the unusual effect of lowering defibrillation energy threshold requirements. Therefore, use of an ibutilide-polyurethane drug delivery system in combination with an implantable defibrillator could significantly enhance the function of the implantable defibrillator. In contrast, intravenously administered ibutilide, used at the same dosages as the cardiac implants, did not have a significant effect in reducing the defibrillation energy threshold. Including an ibutilide-containing controlled release drug delivery system as a component part of implantable defibrillator electrodes, or as an adjunct thereto, would lower the electrical energy requirements to defibrillate the heart. In addition, since ibutilide is a Class III antiarrhythmic agent as well, episodes of ventricular arrhythmias which might lead to ventricular fibrillation would be reduced. Thus, the overall design of an implantable defibrillator with an ibutilide controlled release drug delivery system could be greatly improved over competing systems, since the electrical apparatus would be of a lesser scale, and there would be fewer episodes requiring its active use for defibrillation.

The following examples are additional embodiments which employ the antiarrhythmic agent-containing controlled release dosage forms of the present invention in conjunction with cardiac rhythm controlling devices. As used herein the term "cardiac arrhythmia" covers conditions of abnormal heart rhythm, and specifically includes ventricular arrhythmia, ventricular fibrillation, and superven-

tricular arrhythmias, such as atrial fibrillation, atrial flutter, superventricular tachycardia, multifocal atrial tachycardia, junctional tachycardia, *etc.* Therefore, the term "cardiac rhythm controlling devices" means any device which functions to control heart rhythm by delivering an electrical pulse to the heart, and includes, but is not limited to, implantable cardioverter-defibrillator, countershock and anti-tachycardia pacemakers, overdrive pacemakers, *etc.*

In these embodiments, however, the antiarrhythmic agent may be any agent that functions to control defibrillation and/or tachycardia provided that it does not produce an effect which is otherwise detrimental to the effects of the cardiac rhythm controlling device. The selection of an appropriate antiarrhythmic agent is within the skill of a person of ordinary skill in the art. Polymers loaded with Class III antiarrhythmic agents, specifically ibutilide, sotalol, and artilide, have been observed to significantly lower defibrillation threshold in ventricular arrhythmias, to lower risks of atrial flutter, and to prolong refractoriness and conduction times of ventricular extrastimuli.

Example 15:

In another specific embodiment of the invention, an atrial pacing electrode is coated with an ibutilide-polyurethane as shown in Fig. 21, which is a schematic representation of atrial pacing electrode 20. Atrial pacing electrode 20 has an ibutilide-polyurethane multilamellar coating 21 on end 22 of an electrode body 23. In practice, atrial pacing electrode 20 is implanted in the atrial epicardium during open heart surgery. For acute atrial arrhythmias, the distal end 24 of the pacing electrode is coupled to a lead (not shown) which is threaded through the

chest wall by needle puncture. The lead(s) is electrically coupled to means for applying an electrical current to the heart of the patient. When acute atrial arrhythmia is no longer a risk, typically 10 days after surgery, the pacing electrode can be removed by a simple pull-through maneuver. Of course, atrial pacing electrode 20 can be permanently installed for chronic atrial arrhythmias.

In a preferred embodiment, the following technique is used to form multilamellar coating 21, which is shown in cross-section on the inset to Fig. 21, surrounding electrode body 23:

Formulation 15a:

Ibutilide and Pellathane™ polyurethane (Dow Chemical Company, Midland, MI) were dissolved in THF to form a coating solution. A quantity of ibutilide sufficient to result in 10% wt./wt. drug-loading was used.

In this specific embodiment, an atrial pacing electrode wire lead (~ 100 μm in diameter) was dipped in the above-described coating solution eighteen times to form a well-adhered coating approximately 85 μm thick. The coated wire was ~270 μm in diameter. Of course, the number of layers can be adjusted to produce a coating of any desired thickness. Advantageously, the dip-coating technique results in better adhesion of the polymeric coating to the wire. Moreover, the multilamellar geometry retards the release rate of ibutilide from the polymer matrix. Fig. 22 is a graphical representation of the long term *in vitro* release characteristics of a dip-coated wire fabricated in accordance with Formulation 15a expressed as % cumulative release versus time in days.

The antiarrhythmic and electrophysiologic effects of the ibutilide-polyurethane coated atrial pacing electrode of the present invention were studied in a canine model of atrial flutter. Atrial flutter was induced in dogs following the creation of an intercaval Y-shaped incision on the right atrium in accordance with a modification of the method of Buchanan, *et al.*. J. Cardiovascular Pharmacology, Vol. 33, No. 10-14, 1993; Frame, *et al.*, Circ. Res. Col. 58, pages 495-511 (1986); Wu, *et al.*, Cardiovasc. Res., Vol. 23, pages 400-409 (1991). The Y-shaped incision creates an area of circuitous conduction. Bipolar platinum pacing and recording electrodes were sutured 2 mm apart to the right atrium for atrial pacing and measurement of atrial effective refractory period (AERP). The electrode leads were connected to measuring equipment.

Atrial bipolar signals were amplified with a differential AC coupled amplifier and displayed on an oscilloscope. The recording electrode signal was recorded by a polygraph (Grass Model 79-D, Quincy, MA) and displayed on the oscilloscope. Atrial pacing for determination of refractoriness and the ability to induce atrial flutter was conducted using a Bloom model DTU 110 stimulator (Bloom Associates, Reading, PA) and WPI Model A 385 constant current isolation unit, with pacing at thrice threshold current with a 2.0 ms pulse width.

AERP was determined by pacing at a cycle length of 300 ms and interjecting a single premature stimulus every eighth beat. Each drive cycle was separated by a 2 second pause. The cycle length was shortened by 10 ms decrements until the effective refractory period (ERP) was reached. At ERP, the stimulus failed to capture and produce a propagated response. Atrial flutter was

induced by pacing for 2 to 3 second intervals at cycle lengths starting at 150 ms and decremented by 10 ms to a minimum cycle length of 50 ms. Dogs were considered to have inducible atrial flutter if the arrhythmia persisted for a minimum of 5 minutes. If the arrhythmia could not be initiated in two repetitions of the protocol, the atrial flutter was considered to be non-inducible. The cycle length of atrial flutter was determined by averaging the interval between several atrial electrograms. Atrial flutter was considered to be sustained if it did not terminate spontaneously during measurement and recording of the arrhythmia (about 2 mins.) Sustained atrial flutter was terminated by overdrive pacing at rapid cycle lengths between 50 and 150 ms.

Fig. 23 is a bar graph showing the reduction of atrial flutter inducibility by the ibutilide-polyurethane coated atrial electrodes. During a two hour study period, acute atrial arrhythmias were induced as described above. Following implantation of an ibutilide-polyurethane coated atrial electrode, the inducibility of atrial flutter was significantly reduced ($p < 0.001$; paired T-test). The estimated dose of ibutilide during the two hour study period was about 1 μg/kg. No adverse effects from the drug administration were observed.

Example 16:

Referring to Fig. 24, a schematic representation of yet another specific embodiment of the invention is shown. Fig. 24 shows a pacing-transvenous defibrillator catheter 40 having annular conical tip 41 comprising a silicone rubber matrix containing 30% ibutilide-fumarate by weight made in a manner analogous to Examples 5 and 6. Conical tip 41 and anchoring tines 43 are

configured to engage in the endocardium of the heart of the patient. Fig. 25 is a graphical representation of the release rate of ibutilide from the molded conical tip of Fig. 24. About one year's worth of drug is deliverable from the conical tip.

Pacing-transvenous defibrillator catheter 40 comprises two defibrillator electrodes 42 and 43 disposed on opposite ends of catheter wire 44. Conical tip 41 surrounds a pacing electrode 45 which is disposed on the cardiac-contacting end of pacing-transvenous defibrillator catheter 40 which may be a commercially available model, such as the Endotak Catheter (Cardiac Pacemakers Inc., Minneapolis, MN). In use, the pacing-transvenous defibrillator catheter 40 is installed by cardiac catheterization so that conical tip 41 is in contact with the endocardium and electrodes 42 and 43 lie in a ventricle.

A pacing-transvenous defibrillator catheter of the type shown in Fig. 24 was installed in the anterior left ventricle in a dog. In order to cause fibrillation, an epicardial electrode (Bloom stimulator, Bloom Associates, Reading, PA) was sewn into the left ventricle to deliver an electrical impulse (T = 10 ms). A pair of recording electrodes were placed in the right ventricle to measure electro-physiological changes. Test shocks were delivered in a random sequence to determine baseline defibrillation threshold (DFT). DFT studies were conducted for a 2 hour period post-implantation.

The defibrillation threshold was significantly decreased by use of the pacing-transvenous defibrillator catheter of the present invention. Fig. 26 is a graphical representation of the probability of successful defibrillation by the

pacing-transvenous defibrillator catheter for the application of a 2-20 ms monophasic pulse of energy, measured in joules. Referring to Fig. 26, the control data represents defibrillation of animals in which a control catheter, *i.e.*, no drug-loaded tip, was used. The energy required for 90% success decreased from 10 or more joules predrug to between 3 and 5 joules following implantation of pacing-transvenous defibrillator catheter 40. Similarly, 80% success post-implantation could be achieved with the application of 3 joules or less whereas 10 joules or more were required predrug. No changes in heart rate or arterial pressure were observed. The ibutilide-polyurethane matrix dispensed a 3 μg/kg dose over the experimental period ($p < 0.001$, paired t-tests). Fig. 25 demonstrates that the pacing-transvenous defibrillator catheter of the present invention successfully reduces the energy level required for ventricular defibrillation.

Example 17:

In another embodiment of the invention, an iontophoretic device for epicardial delivery of antiarrhythmic agents in response to electrical signals. In a specific embodiment, a rate-limiting permselective heterogeneous cation exchange member for use in a hollow reservoir iontophoretic device was formulated from a dry conditioned polystyrene cation exchange resin (Dowex 50W, 2X, H^+ form, 200-400 mesh, Sigma, St. Louis, MO) and a medical grade silicone rubber, specifically Silastic Q7-4840 (parts A&B in a 1:1 ratio). The polystyrene cation exchange resin comprised 42% wt./wt. The resulting dispersion was placed in a mold and subjected to a vacuum for 20 minutes to remove air bubbles. Then the mold was compressed at about 1000 pounds of force.

Although the invention has been described in terms of specific embodiments and applications, persons skilled in the art, in light of this teaching, can generate numerous and varied embodiments with these principles without departing from the spirit and scope of the claimed invention. For example, non-pharmacologically active co-cipients are well known in the art, and a person of ordinary skill in the art can select one or more co-cipients for use in the practice of the present invention. Accordingly, it is to be understood that the descriptions in this disclosure are proffered to facilitate comprehension of the invention and should not be construed to limit the scope thereof.

What is claimed is:

1. An arrangement for controlling the heart rhythm of a patient, the arrangement comprising:

electrode means for conducting an electrical signal to or from the heart of the patient; and

implantable controlled release means for releasing a therapeutically effective amount of an antiarrhythmic agent to the heart of the patient.

2. The arrangement of claim 1 wherein said implantable controlled release means comprises a substrate formed of a biocompatible polymeric material incorporating said antiarrhythmic agent therein, said substrate being adapted for direct application to the heart of the patient for effecting transmyocardial delivery of said antiarrhythmic agent.

3. The arrangement of claim 2 wherein said therapeutically effective amount of said antiarrhythmic agent is between about 5% and 40% by weight of said substrate.

4. The arrangement of claim 2 wherein said substrate comprises at least one pharmacologically inert filler having a water solubility characteristic which differs from that of said antiarrhythmic agent.

5. The arrangement of claim 4 wherein the pharmacologically inert filler is selected from the group consisting of inulin, polyethylene glycol, and dimethyl tartrate.

6. The arrangement of claim 2 wherein said biocompatible polymeric material is nonbiodegradable and selected from the group consisting of polyurethane, polydimethylsiloxane, ethylene vinyl acetate, polymethyl methacrylate, polyamide, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polytetrafluoroethylene, and cellulose acetate.

7. The arrangement of claim 1 wherein said electrode means comprises tissue engagement means for engaging the heart tissue of the patient.

8. The arrangement of claim 7 wherein said engagement means is configured as an annular conical tip arranged on a distal end of said electrode means.

9. The arrangement of claim 1 wherein said electrode means further comprises a pacing electrode arranged on said electrode means.

10. The arrangement of claim 1 wherein said electrode means comprises sensing means disposed on a distal end thereof for sensing a predetermined condition of the heart of the patient.

11. The arrangement of claim 1 wherein said electrode means comprises a plurality of defibrillator/cardioverter electrodes.

12. The arrangement of claim 2 wherein said biocompatible polymeric material is biodegradable and selected from the group consisting of collagen, polylactic-polyglycolic acid, and polyanhydride.

13. The arrangement of claim 1 wherein said antiarrhythmic agent is a prolonger of action potential duration and is selected from the group consisting of artilide, clofilium, ibutilide, and sotalol.

14. The arrangement of claim 1 wherein said substrate is in the form of a film.

15. The arrangement of claim 14 wherein the film is multilamellar.

16. The arrangement of claim 1 wherein said substrate is in the form of a molded cardiac contacting component attached to said electrode means.

17. A cardiac rhythm controlling device comprising:

cardiac contact means for conducting an electrical signal to the heart of a living being; and

controlled release dosage means for producing a controlled release of an antiarrhythmic agent.

18. The cardiac rhythm controlling device of claim 17 wherein said controlled release dosage means comprises a substrate of a biocompatible polymeric material which has incorporated therein a therapeutically effective amount of an antiarrhythmic agent.

19. The cardiac rhythm controlling device of claim 17 incorporating a pharmacologically inert filler having a water solubility different from that of said antiarrhythmic agent.

20. The cardiac rhythm controlling device of claim 19 wherein said pharmacologically inert filler is selected from the group consisting of inulin, polyethylene glycol, and dimethyl tartrate.

22. The cardiac rhythm controlling device of claim 17 wherein said biocompatible polymeric material is nonbiodegradable.

23. The cardiac rhythm controlling device of claim 22 wherein said nonbiodegradable biocompatible polymeric material is selected from the group consisting of polyurethane, polydimethylsiloxane, ethylene vinyl acetate, polymethyl methacrylate, polyamide, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polytetrafluoroethylene, and cellulose acetate.

24. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is a prolonger of action potential duration.

25. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is selected from the group consisting of artilide, clofilium, ibutilide, sotalol.

26. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is ibutilide.

27. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is artilide.

30. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is sotalol.

31. The cardiac rhythm controlling device of claim 18 wherein said substrate is in the form of a film adhered to said cardiac rhythm controlling device.

32. The cardiac rhythm controlling device of claim 31 wherein said film is multilammelar.

33. The cardiac rhythm controlling device of claim 31 wherein said film has a thickness on the order of 20 μm to 1 cm.

34. The cardiac rhythm controlling device of claim 18 wherein said substrate is in the form of a molded cardiac contacting component attached to the cardiac rhythm controlling device.

35. A method of treating cardiac rhythm disturbances in a living being have a heart, said method comprising:

placing a polymeric matrix incorporating a therapeutically effective amount of at least one antiarrhythmic agent in direct contact with the epicardium of the heart of the living being in conjunction with a cardiac rhythm controlling device.

36. The method of claim 35 wherein the cardiac rhythm controlling device is an implantable cardioverter-defibrillation device.

37. The method of claim 35 wherein the cardiac rhythm controlling device is an implantable pacemaker.

38. A method of treating or preventing ventricular or atrial fibrillation in a living being having a heart, the method comprising the step of placing a polymeric matrix incorporating a therapeutically effective amount of at least one antiarrhythmic agent of the type which is a prolonger of action potential duration in direct contact with the epicardium of the heart of the living being in conjunction with a cardiac rhythm controlling device.

AMENDED CLAIMS

[received by the International Bureau on 15 July 1994 (15.07.94); original claims 14-35 amended; claims 36-38 cancelled; remaining claims unchanged (3 pages)]

14. The arrangement of claim 1 wherein said substrate is in the form of a film.

15. The arrangement of claim 14 wherein the film is multilamellar.

16. The arrangement of claim 1 wherein said substrate is in the form of a molded cardiac contacting component attached to said electrode means.

17. A cardiac rhythm controlling device comprising:

cardiac contact means for conducting an electrical signal to the heart of a living being; and

controlled release dosage means for producing a controlled release of an antiarrhythmic agent.

18. The cardiac rhythm controlling device of claim 17 wherein said controlled release dosage means comprises a substrate of a biocompatible polymeric material which has incorporated therein a therapeutically effective amount of an antiarrhythmic agent.

19. The cardiac rhythm controlling device of claim 17 incorporating a pharmacologically inert filler having a water solubility different from that of said antiarrhythmic agent.

20. The cardiac rhythm controlling device of claim 19 wherein said pharmacologically inert filler is selected from the group consisting of inulin, polyethylene glycol, and dimethyl tartrate.

21. The cardiac rhythm controlling device of claim 17 wherein said biocompatible polymeric material is nonbiodegradable.

22. The cardiac rhythm controlling device of claim 21 wherein said nonbiodegradable biocompatible polymeric material is selected from the group consisting of polyurethane, polydimethylsiloxane, ethylene vinyl acetate, polymethyl methacrylate, polyamide, polycarbonate, polyester, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polytetrafluoroethylene, and cellulose acetate.

23. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is a prolonger of action potential duration.

24. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is selected from the group consisting of artilide, clofilium, ibutilide, sotalol.

25. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is ibutilide.

26. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is artilide.

27. The cardiac rhythm controlling device of claim 17 wherein said antiarrhythmic agent is sotalol.

28. The cardiac rhythm controlling device of claim 18 wherein said substrate is in the form of a film adhered to said cardiac rhythm controlling device.

29. The cardiac rhythm controlling device of claim 28 wherein said film is multilammelar.

30. The cardiac rhythm controlling device of claim 28 wherein said film has a thickness on the order of 20 μm to 1 cm.

31. The cardiac rhythm controlling device of claim 18 wherein said substrate is in the form of a molded cardiac contacting component attached to the cardiac rhythm controlling device.

32. A method of treating cardiac rhythm disturbances in a living being have a heart, said method comprising:

placing a polymeric matrix incorporating a therapeutically effective amount of at least one antiarrhythmic agent in direct contact with the epicardium of the heart of the living being in conjunction with a cardiac rhythm controlling device.

33. The method of claim 32 wherein the cardiac rhythm controlling device is an implantable cardioverter-defibrillation device.

34. The method of claim 32 wherein the cardiac rhythm controlling device is an implantable pacemaker.

35. A method of treating or preventing ventricular or atrial fibrillation in a living being having a heart, the method comprising the step of placing a polymeric matrix incorporating a therapeutically effective amount of at least one antiarrhythmic agent of the type which is a prolonger of action potential duration in direct contact with the epicardium of the heart of the living being in conjunction with a cardiac rhythm controlling device.

FIG. 1

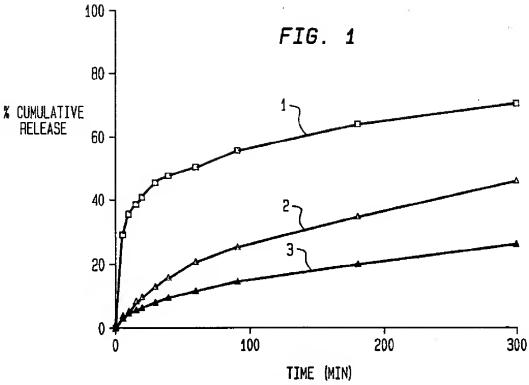

100
80
60
40
20
0
% CUMULATIVE RELEASE
1
2
3
0
100
200
300
TIME (MIN)

FIG. 2

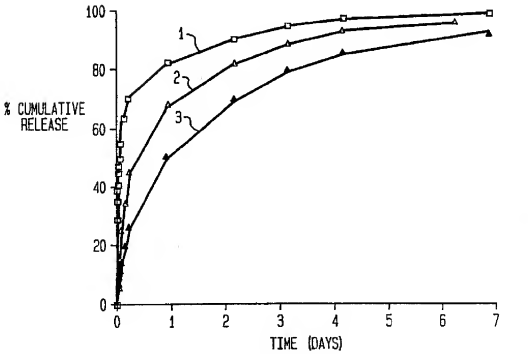

100
80
60
40
20
0
% CUMULATIVE RELEASE
1
2
3
0
1
2
3
4
5
6
7
TIME (DAYS)

FIG. 3

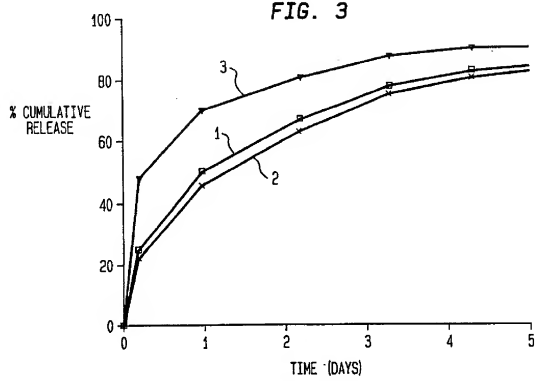

100
80
60
40
20
0
% CUMULATIVE RELEASE
3
1
2
0
1
2
3
4
5
TIME (DAYS)

FIG. 4

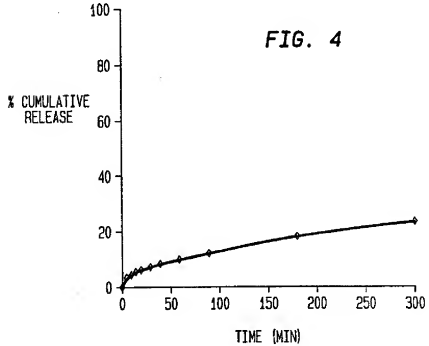

100
80
60
40
20
0
% CUMULATIVE RELEASE
0
50
100
150
200
250
300
TIME (MIN)

FIG. 5

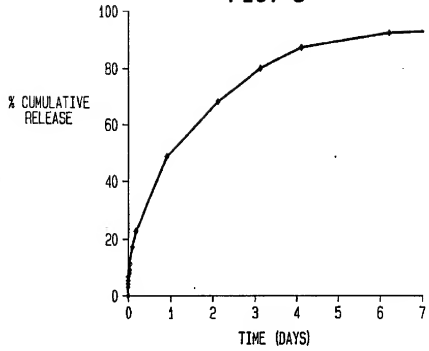

% CUMULATIVE RELEASE
100
80
60
40
20
0
0
1
2
3
4
5
6
7
TIME (DAYS)

FIG. 6

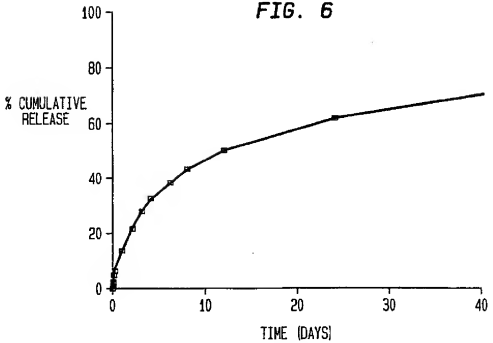

% CUMULATIVE RELEASE
100
80
60
40
20
0
0
10
20
30
40
TIME (DAYS)

FIG. 7

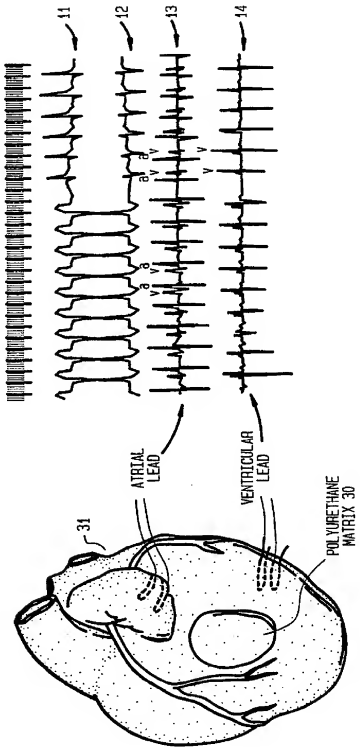


FIG. 8

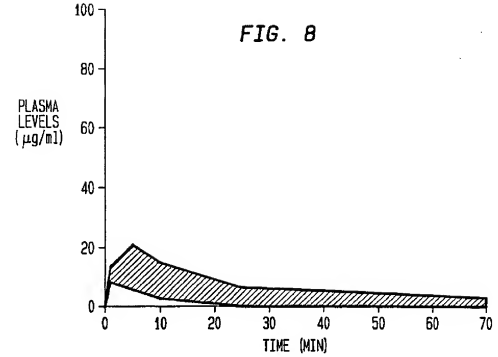


FIG. 9

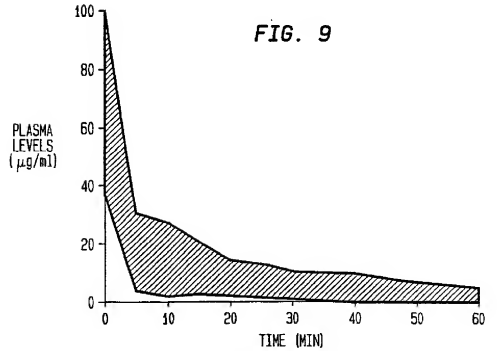
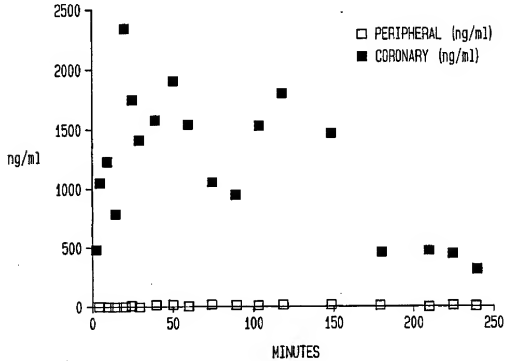


FIG. 10



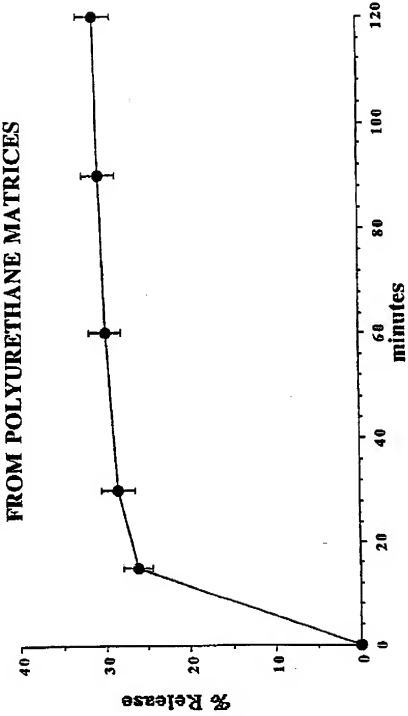

IN VITRO RELEASE OF IBUTILIDE
FROM POLYURETHANE MATRICES
% Release
0
10
20
30
40
0
20
40
60
80
100
120
minutes

FIG. 11

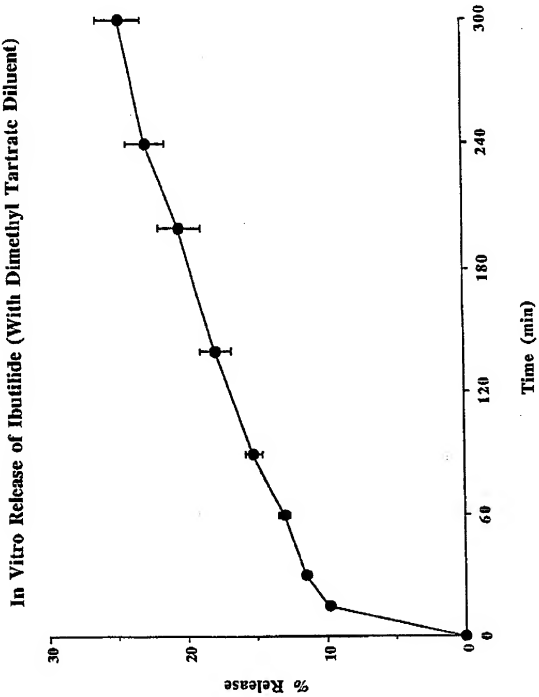


FIG. 12

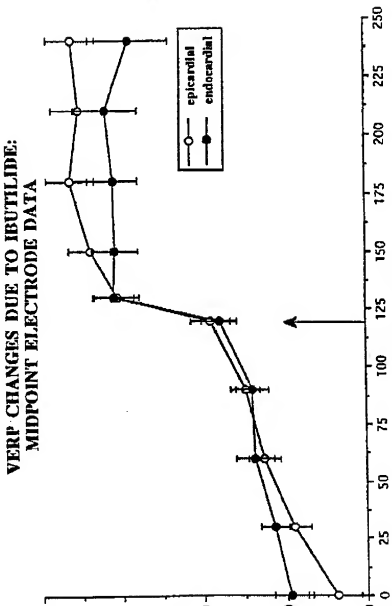

VERP CHANGES DUE TO IBUTILIDE:
MIDPOINT ELECTRODE DATA
epicardial
endocardial
ms
160
150
140
130
120
0
25
50
75
100
125
150
175
200
225
250
minutes

FIG. 13

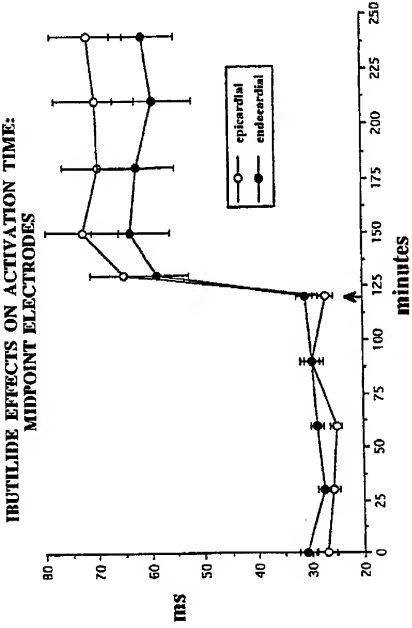

IBUTILIDE EFFECTS ON ACTIVATION TIME:
MIDPOINT ELECTRODES
epicardial
endocardial
ms
minutes
80
70
60
50
40
30
20
0
25
50
75
100
125
150
175
200
225
250

FIG. 14

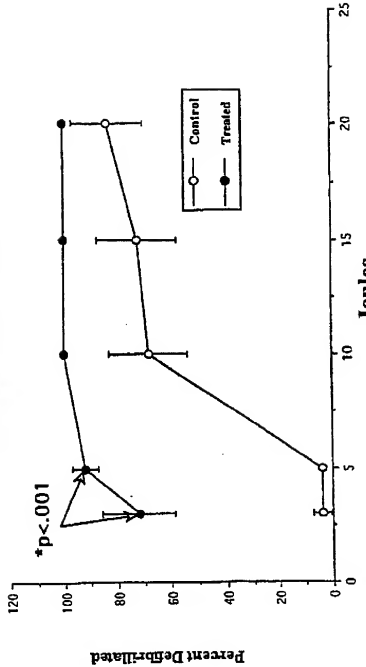


FIG. 15

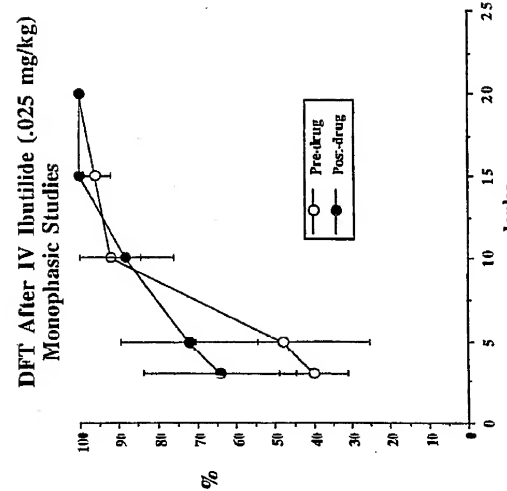


FIG. 16

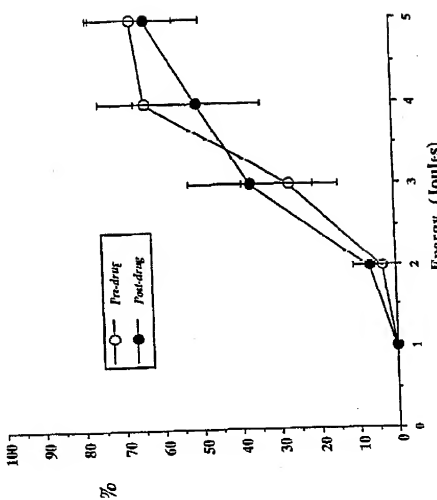

DFT Pre and Post Intravenous Ibutilide
(0.0025 mg/kg)
Pre-drug
Post-drug
%
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
Energy (Joules)

FIG. 17

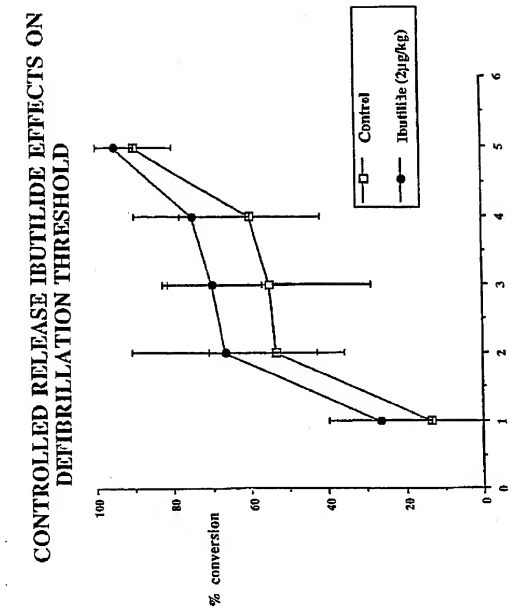


FIG. 18

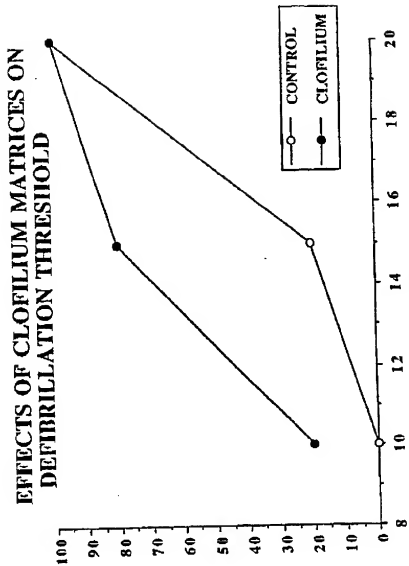

EFFECTS OF CLOFILIUM MATRICES ON DEFIBRILLATION THRESHOLD
% DEFIBRILLATED
100
90
80
70
60
50
40
30
20
10
0
8
10
12
14
16
18
20
JOULES
CONTROL
CLOFILIUM

FIG. 19

CHANGE IN ACTIVATION TIME- IBUTILIDE VS SOTALOL

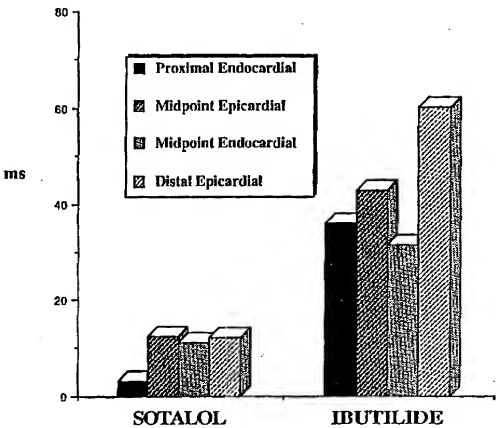


FIG. 20

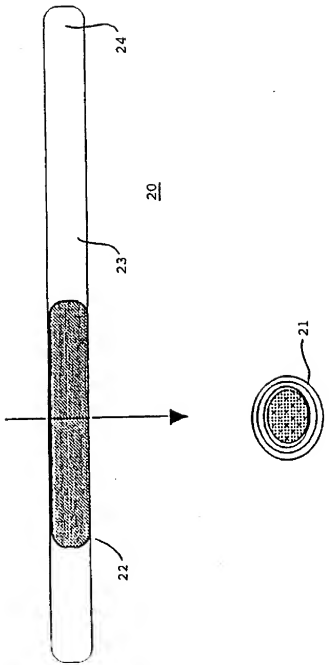


FIG. 21

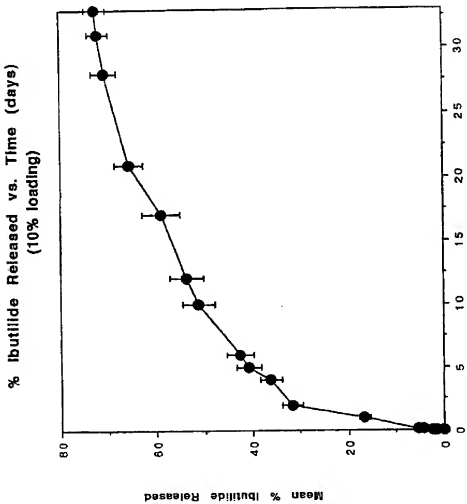

% Ibutilide Released vs. Time (days)
(10% loading)
Mean % Ibutilide Released
0
20
40
60
80
0
5
10
15
20
25
30
Time (days)

FIG. 22

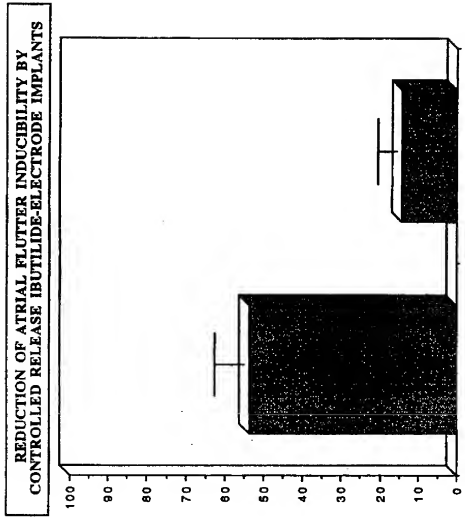

REDUCTION OF ATRIAL FLUTTER INDUCIBILITY BY CONTROLLED RELEASE IBUTILIDE-ELECTRODE IMPLANTS
%
100
90
80
70
60
50
40
30
20
10
0
PREDRUG
POST-DRUG

FIG. 23

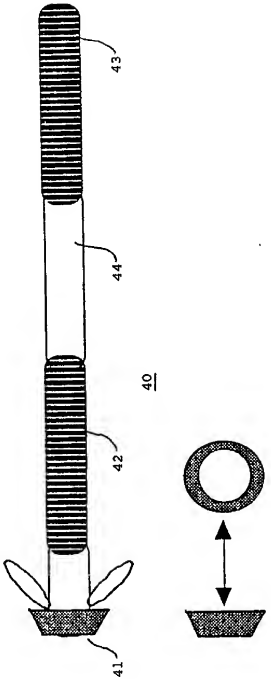


FIG. 24

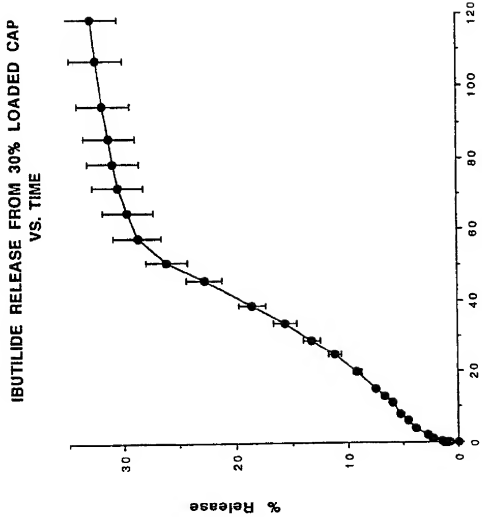

IBUTILIDE RELEASE FROM 30% LOADED CAP
VS. TIME
% Release
0
10
20
30
0
20
40
60
80
100
120
Time (Day)

FIG. 25

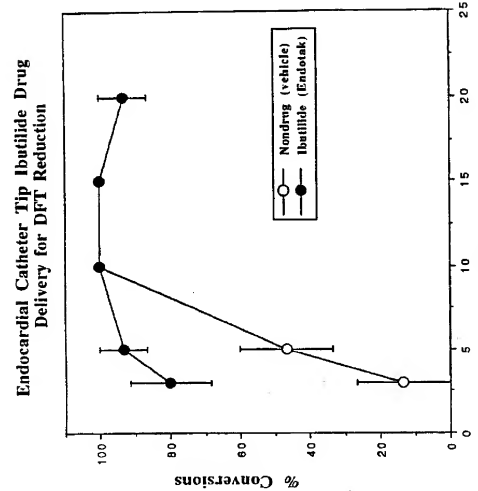

Endocardial Catheter Tip Ibutilide Drug Delivery for DFT Reduction
% Conversions
0
20
40
60
80
100
0
5
10
15
20
25
POWER (Joules)
Nondrug (vehicle)
Ibutilide (Endotak)

FIG. 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02838

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/22; A61B 17/36

US CL :424/423, 424, 425; 514/821, 604/891.1; 607/119, 120, 126, 129

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/423, 424, 425; 514/821, 604/891.1; 607/119, 120, 126, 129

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,506,680 (STOKES) 26 March 1985; see particularly col. 3, lines 13-18 and col. 4, lines 49-58.	1,2,6,7,16-18,22,23,34,35,38. 3,8-13,24-30,36,37
Y	US, A, 4,936,317 (MACGREGOR) 26 June 1990; see particularly col. 13, lines 22-68 and claim 2.	1-38

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 MAY 1994	JUN 29 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer AMY HULINA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-2351

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02838

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 5,154,182 (MOADDEB) 13 October 1992; see particularly col. 3, lines 27-34.	1,2,7,14, 17,18,31, 35, 38 3,6,8-13, 15,16,22-30,32-34, 36,37
X	US, A, 5,087,243 (AVITALL) 11 February 1992; see particularly col. 2, lines 16-40, col. 5, lines 19-41.	1,7-11,17, 18,22,24, 34
X Y	US, A, 5,090,422 (DAHL) 25 February 1992; see particularly col. 3, lines 6-12, 28, 38 and claim 11.	1,2,6,7,9-11,14,15, 17,18,22, 23,31,32, 33,35,36, 3,8,13,16, 24-30,34, 38

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*